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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,169	02/27/2004	Daniel R. Weinberger	NIH222.001C1	9926

20995 7590 10/25/2007

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ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
10/25/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/789,169	WEINBERGER ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,8,10,11,13,14,16,17,19,20,22,23 and 25-51* is/are pending in the application.

4a) Of the above claim(s) *25-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, and 22-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/21/2007 has been entered.

2. Currently, claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, 22-23, and 25-51 are pending in the instant application. Claims 25-51 are withdrawn from consideration as being drawn to non elected inventions. Claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, and 22-23 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non-FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 2, 5, 8, 11, 14, 17, 20, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims have been amended to recite "...verbal memory, assayed with memory scores...". This recitation is indefinite as the use of the term "score" is unclear. It is not clear if the term is meant to be directed to a measurement of a memory task, or whether it is a particular type of memory task.

Response to Arguments

5. The response traverses the rejection and asserts that the expression "memory scores" would have been understood as meaning a measurement of hippocampal dependent verbal memory, for example by using the WMS-R test. This argument has been thoroughly reviewed but was not found persuasive as the specification is silent with regard to what memory tests were used and there is no evidence presented that the WMS-R test is the only test of hippocampal dependent verbal memory. Regardless of such, if the term 'score' is taken as a "measurement", then the claims literally read "assayed with memory measurements". However, in this situation, it appears that applicants intend the term to be the measured result or value result of the test. Therefore, it is unclear how the test or 'assay" is performed with a measured result. The arguments that the term would have been understood by one possessing the ordinary level of skill of the pertinent art as meaning a measurement of hippocampal dependent verbal memory is not found persuasive as the specification does not teach the specific tests used or that the test was particular a measure of hippocampal dependent verbal memory. The arguments with regard to Kopelman et al; 1998 as well as the reference have been thoroughly reviewed but were not found persuasive as Kopelman does not appear to provide any specific discussion of the CVLT test vs the WMS-R test or to teach "The CVLT was considered to have a larger 'prefrontal

component'... excluding it as a test of hippocampal dependent verbal memory", nor does the response provide any specific citation within the reference to support this conclusion.

6. Claims 2, 5, 8, 11, 14, 17, 20, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

The amendment to recite "hippocampal dependent verbal memory" does not appear to be supported by the specification. At para 0008, the specification asserts that in cohorts, "the met allele had abnormal patterns of hippocampal activation while performing memory tasks", however the specification is silent as to which memory tasks were administered and it is not clear that the effect of the met allele on verbal memory was 'hippocampal dependent'. Accordingly, the amendments appear to have introduced new matter into the claimed invention.

Response to Arguments

7. The response traverses the rejection. The response asserts that there is exact antecedent basis for "hippocampal dependent verbal memory". This argument has been thoroughly reviewed but was not found persuasive as the specification does not recite this phrase. The response cites "appears to involve hippocampal (HIP) abnormalities, including deficits in verbal memory" in para 0008 as support. This paragraph as well as the arguments have been thoroughly reviewed but were not found persuasive. The sentence cited in the response is with regard to schizophrenia, which as the response notes the met and val allele are not indicative of

schizophrenia. Further, the specification notes "hippocampal abnormalities, including deficits in verbal memory", however it does not state that the impaired or enhanced verbal memory is hippocampal "dependent". The association between hippocampal abnormalities and verbal memory is unclear, nor does the specification, anywhere in para 0008 make clear: which verbal tests were used, or that the verbal memory tests were hippocampal dependent. Portions of para 0008 of the specification contemplate that the polymorphism is associated with schizophrenia, which, as noted previously, it has been determined that the met66val allele is not associated with schizophrenia. Of further note, the specification teaches "BDNF met66val accounts for genetic variance in human hippocampal function and verbal memory". It is not clear from this recitation that the term "and" is meant to signify that the verbal memory is hippocampal dependent. Rather, it appears that variance was found in both hippocampal function and verbal memory, not a specific subtype of verbal memory. Further, since the specification is completely silent as to which verbal memory tests were performed, the amendment to specifically state that the impairment was to "hippocampal dependent verbal memory" is not supported by the specification. Nowhere does the specification indicate, for example, that the WMS-R test was performed.

8. Claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient

evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims (1 and 2) are drawn to a method of predicting the likelihood that a human will have impaired or enhanced hippocampal function assayed with fMRI or impaired or enhanced hippocampal dependent verbal memory, assayed with memory scores, by obtaining a DNA sample and determining the presence or absence of a single nucleotide polymorphism (SNP) G to A resulting in the substitution of a methionine for a valine (G=Val, A=Met) at amino acid position 66 relative to the start of the precursor protein sequence in BDNF, wherein the presence of a G to A polymorphism resulting in a methionine residue at position 66 is indicative of the likelihood that the human will have impaired hippocampal function, assayed with fMRI, relative to valine, or impaired hippocampal dependent verbal memory, assayed with memory scores, relative to valine, and wherein the presence of an A to G resulting in a valine residue at position 66 is indicative of the likelihood that the human have enhanced hippocampal function, assayed with fMRI relative to methionine, or enhanced hippocampal dependent verbal memory, assayed with memory scores, relative to methionine. The claims (13 and 14) are also drawn to a method of predicting the likelihood that a human will impaired or enhanced hippocampal function,

assayed with fMRI, or impaired or enhanced hippocampal dependent verbal memory, assayed with memory scores by obtaining a biological sample containing the precursor BDNF protein or relevant portion thereof and determining the amino acid present at position 66 relative to the first amino acid of the precursor protein wherein the presence of a methionine residue at position 66 is indicative of the likelihood that the human will have impaired hippocampal function, assayed with fMRI relative to valine, or impaired hippocampal dependent verbal memory, assayed with memory scores relative to valine, and wherein the presence of a valine residue at position 66 is indicative of the likelihood that the human have enhanced hippocampal function, assayed with fMRI relative to methionine, or enhanced hippocampal dependent verbal memory, assayed with memory scores relative to methionine.

The claims are further limited to humans that are at risk for development of impaired hippocampal function, or impaired hippocampal dependent verbal memory (claims 4-5, 16, 17). The claims are also further limited to individuals that exhibit clinical symptomology associated with (claims 7-8, 19-20) or individuals that are clinically diagnosed as having (claims 10-11, 22-23) impaired hippocampal function, or impaired hippocampal verbal memory.

The nature of the invention, therefore, requires the knowledge of a predictive association between the presence of an A/met or G/val at codon position 66 of BDNF and impaired or enhanced hippocampal function, or impaired or enhanced hippocampal dependent verbal memory.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that BDNF is a neurotrophin and contains at least one known nonconservative SNP producing a met66val substitution (page 3). The specification teaches that verbal memory was assessed in 184 patients with schizophrenia, 283 siblings, and 101 controls and that NAA (N acetyl aspartate) was available for 110 subjects (page 4). The specification teaches that the effect of genotype was significant across all groups for memory scores ($p<.008$) and that the met allele was associated with poorer performance. However, the specification teaches that BDNF genotype had no effect on IQ or prefrontal cognitive measures.

The specification teaches that the met allele was associated with reduced hippocampal NAA ($p<.07$), however this result does not appear to be statistically significant. The specification further teaches that in two separate cohorts studied with fMRI, subjects with the met allele had abnormal patterns of hippocampal activation while performing memory tasks, compared to val/val homozygote subjects. The specification, however does not teach if this was statistically significant (page 4). Although the specification suggests that the met allele may be associated with impaired hippocampal function or impaired verbal memory, the specification does not provide any guidance or working examples that the val allele alone is predictive of the likelihood that a human will not have impaired verbal memory or impaired hippocampal function. Bath (Bath and Lee, Cognitive, Affective & Behavioural Neuroscience, 2006, vol. 6, pages 79-85) teaches that the effect of the met66val polymorphism is different in various ethnicities (page 81, col 2, last para). Accordingly, it does not appear that the presence of the val allele would be necessarily indicative that a human will have enhanced hippocampal function or verbal memory. The specification provides no working examples of human subjects and controls

demonstrating that the val allele is associated with enhanced hippocampal function or verbal memory than in normal controls.

The claims encompass analysis in any human individual, which includes any human population. The specification provides no working examples of associations studies between the indicated alleles and different ethnic populations.

The state of the prior art and the predictability or unpredictability of the art:

Although the specification sets forth a number of substantially different hypothesis (page 9, para 0022) the specification does not teach the effect of val66met SNP on BDNF function. The association between the polymorphism and its effect on hippocampal function, verbal memory, and disorders involving impaired memory are unclear. The art at the time the invention was filed, does not make up for the deficiencies in the specification. Association of the met or val allele at codon 66 of BDNF with hippocampal function, verbal memory and disorders involving impaired memory, such as schizophrenia, or Alzheimer's disease (AD), in different populations is highly unpredictable as exemplified by the teachings in the art.

The post filing date art of Neves Pereira (Neves-Pereira et al; Molecular Psychiatry, vol. 10, pages 208-212, 2005) teaches that although the val66met polymorphism has been shown to alter gene function, the risk may depend on the haplotypic background on which the val/met variant is carried (see abstract). As evidenced by the haplotype analysis for SNPs in BDNF, Sklar (Sklar et al; Molecular Psychiatry, vol. 7, pages 579-593, 2002) teaches that 8 BDNF SNPs, including the val66met (a39) polymorphism are found in 6 different haplotypes, which are found at different frequencies in different populations (see table 4). The study of Neves Pereira

contradicts the teachings of the specification in that it teaches that the valine allele, as opposed to the methionine allele as disclosed in the instant application, is associated with schizophrenia in a Scottish population (see abstract). Likewise, Kent (Kent et al; Molecular Psychiatry, vol. 10, pages 939-943, 2005) teaches that the valine allele was found to be preferentially transmitted in ADHD (see abstract) and Ventriglia (Ventriglia et al; Molecular Psychiatry, 2002, vol. 7, pages 136-139) teaches that the homozygosity for the valine allele appears to confer an increased risk for AD (see page 137, first col).

Alternatively, Zhang (Zhang et al; American Journal of Medical Genetics, Part B, vol. 141B, pages 387-393, 2006) teaches that there was no association found for the val66met polymorphism and AD, affective disorders, or schizophrenia. Jonsson (Jonsson et al, Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 30, pages 924-933, 2006) teaches that there were no significantly different allele, genotype, or haplotype frequencies between patients with schizophrenia and controls for the BDNF val66met SNP and teaches that further studies are needed to establish risk with schizophrenia (see abstract). Antilla (Antilla et al; J. Neural Transm, vol. 112, pages 885-890, 2005) teaches that a study by Egan et al, 2003 (applicants own work) showed that the BDNF G196A polymorphism was not associated with schizophrenia, but that a study by Hong et al 2003 reported that the val/val genotype was slightly more common in schizophrenia patients, at opposite with the teachings of the instant specification. Antilla teaches that in a study of Finnish patients, the G196A (val66met) polymorphism was not associated with risk of schizophrenia, treatment response, or age of onset (see pages 888-889). Further, Antilla teaches that previous studies have suggested that the frequency of val66met polymorphism is different in different ethnic populations. In line with

this teaching, the post filing date art of Bath (Bath & Lee, Cognitive, Affective, & Behavioral Neuroscience, vol. 6, pages 79-85, 2006) exemplifies the unpredictability of correlating hippocampal function, verbal memory, or disease risk in different populations, as is broadly encompassed by the claims. Bath teaches that cognitive and behavioral effects associated with the methionine allele have been shown to produce much more robust effects in Caucasians (page 81, col. 1, 2nd full para). Bath teaches that the methionine allele is not uniformly distributed across all ethnicities or all regions of the world and that Northern Europeans appear to be much more affected than Asian populations, despite the fact that a higher proportion of the Asian population carry this allele, suggesting that some ethnicities may compensate for the variation in the BDNF gene through some as yet unidentified mechanism and are thus less affected by the presence of the polymorphism (see para bridging pages 81-82).

The claims (13-14, 16-17, 19-20, 22-23) are also drawn to assessing the precursor protein and determining the amino acid present at position 66, thus encompassing analysis of the BDNF protein (page 6, para 0013), using for example, antibodies that bind to one form of the gene product but not another (page 10, para 0025). However, neither the art nor the specification teach an antibody that is capable of specifically differentiating the BDNF valine66 from the BDNF methionine66 variant. It is unpredictable whether the amino acid change would be sufficient to result in the production of antibodies that can differentiate between the two molecules. In some cases, an antibody elicited by one antigen can cross-react with a different antigen if the two different antigens share an identical or very similar epitope (Goldsby et al., 2003, p. 141). Thus, absent knowledge of the binding epitopes and the effects of the instant polymorphism on those epitopes, it is difficult to predict whether or not any generated antibody

will be able to function to differentiate the two alleles in an assay. In the instant case, it is unpredictable as to whether or not an antibody would be able to differentiate between the two variants, a feature that is encompassed by the claimed invention.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

In order to practice the invention as broadly as it is claimed, one would first have to establish that a predictive relationship exists between the val66met polymorphism and impaired or enhanced hippocampal function, including as assayed by fMRI, or impaired or enhanced hippocampal dependent verbal memory, assayed by memory scores. The skilled artisan would then be required to determine if this relationship existed in *any* population. Given the conflicting results in the specification and the art as to a predictable association between the valine and methionine allele and different disorders or cognitive affects in different populations, as well as the conflicting teachings of the art (e.g., see Egan 2003, addressed below in response to applicant's traversal citing Egan) such analysis would be replete with trial and error experimentation, the results of which are completely unpredictable. Given the teachings of the art that the affects of the allele appear to be influenced by the genetic background it is found in, the results of such analysis are completely unpredictable, as neither the specification, nor the art at the time of filing, teach how the allele is associated with the claimed phenotypes. It was not known whether the alleles themselves are functionally associated, or linked to some functionally

associated alteration hundreds or thousands of nucleotides away. Additionally, given the teachings of Goldsby, unpredictable trial and error experimentation would be required to practice the invention as broadly claimed with regard to protein analysis, additionally required for claims 13-14, 16-17, 19-20, 22-23.

Therefore, in light of the breadth of the claims, the conflicting guidance in the specification, the high level of unpredictability in the art as exemplified by the numerous studies which provide conflicting data regarding associations with val66met allele with various phenotypes, the nature of the invention, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to make or use the invention as broadly claimed.

Response to Arguments

9. The response traverses the rejection. The arguments as well as the declaration filed under 37 CFR 1.132 by Dr. Weinberger have been thoroughly reviewed but were not found persuasive to overcome the rejection.

At page 2, the declaration reiterates the claims 1, 2, 13, and 14. At section 4.a.i, the declaration summarizes certain portions of para 0008 of the specification which appear to be relevant to instant claims 2 and 14. At section 4.a.ii, the declaration states that MPEP 2164.05 sets forth that "applicant may provide a declaration after the filing date that demonstrates that the claimed invention works" and cites Egan et al., Cell 112:257, 2003. Regarding MPEP2164.05, it is noted that the guidance sets forth:

> "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed

> invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention"

The response asserts that Egan 2003 demonstrates that BDNF plays a role in hippocampal function and verbal memory in humans. The declaration cites a first experiment and states "Patients with schizophrenia had substantially lower scores compared to controls, while siblings were intermediate between these groups, consistent with earlier reports" and cites Egan et al; PNAS 98:6917, 2001. Egan 2001 has been thoroughly reviewed, however there does not appear to be nexus between the teachings of Egan 2001 and the claims and specification of the instant invention. Notably, Egan 2001 provides analysis of a different gene and mutation, and uses, for the example, the WCST test, whereas the instant specification is silent as to which memory tests were performed. The declaration further states that Egan 2003 shows BDNF genotype had a significant effect on memory scores in the entire sample as well as the controls and that met/met homozygotes had lower scores compared to val/val and val/met. This argument as well as Egan 2003 have been thoroughly reviewed but were not found persuasive to overcome the rejection as the claims require the detection of only a single met allele, which encompasses met/val heterozygotes, whereas it appears that the post filing date art is teaching that met/met homozygotes was the group that showed a significant effect. Accordingly, the claims do not bear a reasonable correlation to the scope cited in the post filing date art. Additionally, the instant specification does not teach or provide guidance with regard to results of met/met homozygotes vs val/val and val/met heterozygotes, nor does this information appear to have been

well known to one of skill in the art at the time the invention was filed. Further, the assertion that each genotype was well matched on a variety of demographic parameters and the discussion with regard to the WMS-R test and immediate recall scores is not supported by the teachings in the specification which is silent with regard to steps, materials, and conditions for the experiments. Notably, the specification is silent with regard to the different memory tests used in Egan 2003, the sample size in the specification appears smaller than that cited in Egan 2003, the specification is silent with regard to the statistical analysis with regard to homozygosity or heterozygosity of the met/val polymorphism in certain tests, and the specification is silent with regard to the ethnicities of the subjects assayed in the study. The declaration then summarizes results with a second memory test from the Egan 2003 paper, the CVLT test, and asserts that "the CVLT is considered to have a larger 'prefrontal component'[citing Kopelman 1998]... compared to WMS-R, thus excluding it as a test of verbal memory that is hippocampal dependent, and leaving the WMS-R as a valid test of hippocampal dependent verbal memory". This argument as well as the Kopelman reference have been thoroughly reviewed, however as noted previously, Kopelman does not appear to provide any specific discussion of the CVLT test vs the WMS-R test or to teach "The CVLT was considered to have a larger 'prefrontal component'... excluding it as a test of hippocampal dependent verbal memory", nor does the response provide any specific citation within the reference to support this conclusion. Additionally, it is noted that Egan 2003 states "The CVLT may have a larger 'prefrontal component' compared to the WMS-R, possibly reducing hippocampal and val66met related variance" (page 258, col.2), rather than the definite assertion made in the present declaration. It is not clear, therefor, that one of skill in the art would necessarily come to the conclusion that

only the WMS-R test is a valid test of hippocampal dependent verbal memory. Again, the Kopelman 1998 reference was thoroughly reviewed but such specific conclusions do not seem to be asserted in the reference. At section 4b, the declaration discusses IQ and Prefrontal Cognitive measures, however it is not clear what nexus, if any, this section has to the pending claims.

At section 4.c.i, the declaration summarizes a portion of para 0008 from the specification, which appears to be relevant to claims 1 and 13. At section 4.c.ii, Citing Egan 2003, the declaration reiterates the teachings of Egan 2003, page 258, col. 2-page 260, "Effect of BDNF genotype on Hippocamal Activation" as well as figure 2. Notably, the declaration discusses an in vivo assay of hippocampal physiology using blood oxygenation level dependent fMRI technique in subjects performing the N-back working memory task. However, the specification is silent as to which tests were used, nor is it clear that one of skill in the art would have been able to determine which test was being used. Again, as noted previously, Egan 2003 teaches steps, materials, and conditions which are not supported in the specification. Further, regardless of such issues, both Egan 2003 and the specification do not provide analysis that takes into account different ethnic populations, although the post filing date art of Bath teaches is important. Bath specifically addresses the unpredictability of the effect of the met/val polymorphism in different ethnicities. Bath teaches "It is still unclear what these findings mean for a broader population... the Met allele is not uniformly distributed across all ethnicities or all regions of the world... northern Europeans appear to be much more affected than Asian populations despite the fact that a higher proportion of the Asian population carries this [Met] allele." At section 4d, the declaration assets that "because we see identical effects in one ethnic group alone (European Americans) and because similar effects re seen in both normal and

controls and our schizophrenic families, said ethnicities should be equally affected by the presence of the polymorphism". This statement has been thoroughly reviewed but was not found persuasive as it is unclear how results from a single population would provide any indication as to the possible effect of the polymorphism in a different ethnic population when it is known that differences exist between the two populations regarding the BDNF met66val allele. The declaration confirms that the results were only evaluated in a European Americans and is silent with regard to how this would affect Asians when the art provides evidence that "northern Europeans appear to be much ore affected than Asian populations despite the fact that a higher proportion of the Asian population carries this [Met] allele".

At section 5, the declaration asserts that "we did not find evidence that BDNF was associates with increased risk for schizophrenia" which is puzzling as 1) the specification asserts that such an association exists, and b), the claims no longer recite this embodiment. Further, with regard to the assertions that the met allele may affect other human illnesses, it is noted that the office action provides evidence of conflicting data in a number of prior and post filing date references with regard to associations with BDNF Met66Val polymorphisms in different diseases or disorders.

At section 6, the declaration corroborates the instant rejection's statement that the level of skill in the art was high. At section 7 the declaration cites Sambrook 1989 and Ausubel, 1989 for conditions, Egan et al, Biological Psychiatry 2001and Weickert 2000 for Neuropsychological tests, Callicot 2000 and Ogawa 1992 for Hippocampal function, and Harlow and Lane 1988, "Antibodies" for "Antibodies that specifically recognize the BDNF valine 66 but not the BDNF methionine66 variant, as well as Zho et al 2004. These references have been thoroughly

reviewed but were not found persuasive to overcome the rejection as none of the references provides the specific steps, materials, and conditions that were used in the instantly filed application. Although they provide a general discussion of such conditions, steps, or materials, taking this prior art as a whole, the skilled artisan would not have been able to predict which specific steps, conditions, and materials were used in the instantly filed specification or the Egan 2003 reference. Additionally, the ability of the ordinary artisan to make an antibody that specifically recognized the val vs met variant appears to be dependent on whether the variants produced epitopes that were different enough to be distinguishable using antibodies, as noted by Goldsby. Thus, absent knowledge of the binding epitopes and the effects of the instant polymorphism on those epitopes, it is difficult to predict whether or not any generated antibody will be able to function to differentiate the two alleles in an assay.

For these reasons and the reasons already made of record, the rejection is maintained.

10. Claims 1, 2, 4, 5, 7, 8, 13, 14, 16, 17, 19, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by SklarII (Sklar et al; US Patent 6,458,541).

The claims have been re-reviewed. With regard to claims 1, 2, 13, and 14, the recitation of "wherein a single nucleotide polymorphism... is indicative of the likelihood that a human will have..." and "wherein the presence of a methionine [valine] at this position is indicative of the likelihood that a human will have..." merely recite properties of the polymorphism, which are inherent to the polymorphism itself. Accordingly, the only active step set forth in the claim is the steps of obtaining a DNA sample [or biological sample] and determining the presence of a single nucleotide polymorphism or amino acid at the particularly named positions.

Sklar II teaches obtaining a DNA sample and detecting an A/G SNP at position 424 in the sequence encoding the BDNF precursor protein in patients with bipolar disorder as well as neuropsychiatric disorders, such as schizophrenia, ADD (see col. 1, lines 30-35, lines 55-60, Figs 1A and 1B; para bridging cols 14 and 15). Sklar II teaches that this SNP encodes a val/met change in the encoded protein. It is noted that this position corresponds to the position recited in the instantly claimed invention. Sklar II further teaches obtaining a sample and detecting the val/met amino acid in the encoded protein (col 2, lines 56-col. 3). With regard to claims 4, 5, 7, 8, 16, 17, 19, and 20, the patient population taught by Sklar II is inherently "at risk for" and exhibits "clinical symptomology associated with" the claimed phenotypes as bipolar disorder involves hippocampal function and verbal memory as well as impaired memory. Accordingly, the teachings of SklarII anticipate the instant claims.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Jehanne Sitton/
Primary Examiner
Art Unit 1634
October 18, 2007